

NETL EXTERNALITIES WORKSHOP
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WHAT TYPES OF PM_{2.5} ARE MOST
LIKELY TO BE HARMFUL? CAUSE
NEGLECTIBLE HARM?

SOME RESEARCH SUGGESTIONS

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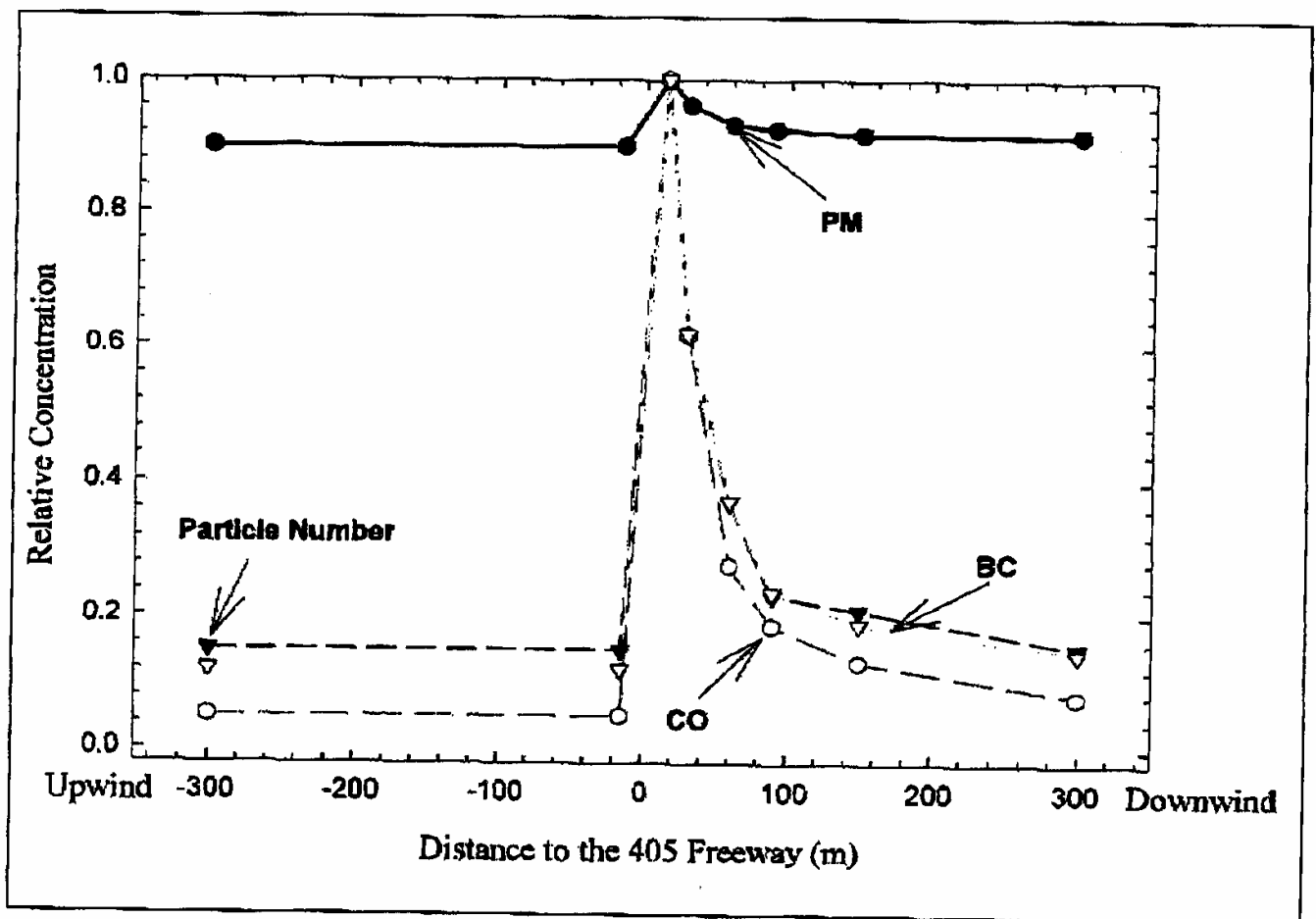
Introduction: New studies show that:

- Highway pollutants can vary by a factor of 10 to 20 within a hundred yards in urban areas
- The relative risk of cardiopulmonary mortality within these hundred yards is almost doubled
- This relative risk (1.95) is over 15 times higher than for cardiopulmonary mortality in similar, “single monitor” studies such as the ACS study (1.06), which themselves state that they cannot distinguish within-locality pollution differences
- These findings suggest the possibility that very local pollution *may* account for much to

most of the premature mortality in PM_{2.5} studies

- Need to know what pollution components are responsible: tremendous research need

“A” Frame of Highway Pollutants



DOE's PM2.5 RESEARCH SUGGESTIONS (1)

DOE suggests a research focus on the following areas:

- (1) A “Structured Regulatory Toxicology Program,” designed to answer regulatory questions, e.g., which types of PM2.5 are more likely to cause premature mortality? Or have negligible effects?

DOE's PM2.5 RESEARCH SUGGESTIONS (2)

How would a “Structured Regulatory Toxicology Program” work?

- Test *many PM2.5 types*, mixtures, as typically found in ambient air
- Use *same multiples* of ambient concentration of each in tests (e.g., 10 times, 50 X, 200 X, 800 X, 2500 X)
- Test against *several of the toxicological endpoints* deemed most likely to be causally linked to adverse impacts (e.g., cardiopulmonary mortality) in humans
- PM2.5 types which cause adverse effects at low levels would be seen as more dangerous than those causing effects at higher levels

HOW STRUCTURED TOXICOLOGY MIGHT HELP: QUICK EXAMPLE (1)

* *In vitro* cellular tests can provide important information, but don't demonstrate what may cause premature mortality at ambient levels

--- Example: Fernandez, et al inhalation study ("Resuspension of coal...generated fine particles...", Science of the Total Environment, 2002) found that inhalation of 3,000 ug/m³ coal ash did not result in lung injury suggested by earlier *in vitro* tests, which found potential lung injury biomarkers:

--- *what happens in the test tube might not be relevant to what happens in the body*

* *In vivo* installation and inhalation animal tests at several thousand to 10s of thousands X ambient levels have little relationship to ambient levels...but a *negative* finding could be useful

* *In vivo* inhalation at levels not far from ambient more likely to reflect actual harm

HOW STRUCTURED TOXICOLOGY MIGHT HELP: QUICK EXAMPLE (2)

Health Effects Institute Research Report # 112
("Health Effects of Acute Exposure to Air
Pollution", Dec. 2002):

"Many studies have found *in vitro* changes in inflammatory markers in cells exposed to high concentrations of diesel exhaust and other particles, *but studies in animals and humans are needed to indicate whether exposure to particles at concentrations reflecting ambient exposure levels causes changes in inflammatory markers in the lung.*" (HEI statement, pg.2)

DOE's PM2.5 RESEARCH SUGGESTIONS (3)

(2) Highway emissions -- need to research:

- a. Are we seriously underestimating mortality near major roads? New studies show almost double the risk for those living within 100 M of major thruway, 50 M of major urban road
- b. Is CO partly responsible for mortality attributed to PM2.5, for both chronic and acute effects?
- c. Ultrafines (like CO, drop off very sharply with distance (< 100 M) from highways)

(3) Wood smoke: Toxicology and ambient levels

- a. Ambient levels in different parts of U.S.?
- b. Need much more info on toxicology, but work to date suggests possible mortality effects at near ambient levels inside home

PM2.5 RESEARCH ISSUES

Main Scientific Issue: Does all PM2.5 have roughly the same effects – does it all contribute to premature mortality at current ambient levels?

Or are some constituents relatively toxic, others relatively innocuous at current ambient levels?

Answer appears to be that specific constituents of PM2.5 are crucial to effects, but these fractions not yet identified...

EVIDENCE FOR DIFFERENCE AMONG PM2.5 IN TOXICITY

(1) Godleski, et al (HEI, 2000) *in vivo* testing of concentrated PM2.5 (CAPs) on animals:

On ~ 25% of the days, there was no impact on HRV, heart rate, or other parameters – study states failure to respond due to lack of PM toxicity, despite higher PM2.5 mass, higher sulfate levels

(2) Creason, et al (J. Exposure Analysis and Env. Epid., 2001) study of heart rate variability in elderly:

On 2 days (including peak PM2.5 day [$> 50 \text{ ug/m}^3$], third highest PM day following), there was no effect: trajectory indicated air mass from rural PA. – study suggests lack of effect due to different PM2.5 composition.

(3) Ghio/Devlin (Am. J. Respir. Crit. Care Med, 2001) *in vivo* installation study of lung injury:

“...mass may not be the most appropriate metric...in assessing health effects...specific components must be identified and assessed.”

NATIONAL ACADEMY OF SCIENCE RECOMMENDATIONS (1998)

NAS sees need to understand toxicity of different PM_{2.5} constituents:

- * NAS (National Research Council) 1998 report: Without “a better understanding of how particulates affect health,” planned monitoring system “might not measure the most hazardous air particles of the most serious exposures.”
- * “The committee recommends that EPA consider more fully the possibility that the expensive monitoring program is not measuring the most biologically important aspects of particulate matter.”
- * NAS also suggested that EPA: “Investigate the toxicological mechanisms by which particulate matter produces mortality...using laboratory animals, human clinical studies, and *in vitro* test systems.”

OTHERS SUGGEST NEED FOR UNDERSTANDING WHICH PM2.5 CONSTITUENTS ARE MOST TOXIC

* New England Journal of Medicine Editorial:

- “An aggressive research program to identify the harmful components of PM2.5, their sources, and the mechanisms of their effects offers the best hope for developing more focused regulatory strategies that will simultaneously protect the public health and the nation’s prosperity.” (12/12/2000)

* CASAC “Closure letter” (6/13/1996):

“...many unanswered questions and uncertainties associated with establishing causality of the association between PM2.5 and mortality....The concerns include:...the lack of an understanding of toxicological mechanisms, and the existence of possible alternative explanations.”

EPIDEMIOLOGY: HIGHWAY EMISSIONS CAUSE HIGH MORTALITY?

New study (Lancet online: Oct. 19, 02):

“Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study” (Hoek et al):

- Extremely large risk of mortality from cardiopulmonary disease for those living within 100 M of freeway, or 50 M of major urban road (relative risk of 1.95, vs. 1.06 for ACS study, also for CPD, for 10 ug/m³ PM_{2.5} increase)
- No signif. risks for other mortality endpoints
- Cohort study (1986), participants over age 55
- Black smoke, NO₂ were measured pollutants: but ultrafines known to be high this close to major roads; CO not measured, however
- NO₂ role discounted because much higher in homes (when cooking)

EPIDEMIOLOGY: HIGHWAY PM AND GASES DROP PRECIPITOUSLY WITH SMALL DISTANCE FROM ROADWAYS

Two new studies from UCLA show that particle mass, ultrafines (especially) and CO drop off very quickly within short distance of major U.S. highways (Zhu, Y., et al, in J. Air & Waste Manage. Assoc., 2002, and in Atmospheric Environment, 2002)

- * Levels drop precipitously from 17 to 90 to 300 meters: CO drops by 5 and 10 times; black carbon by 3 and 5 times)

- * Up to 30 times fewer ultrafines by 165 feet distance downwind

- * Relevance: high relative risk of mortality for those living near highways, urban arterials (observations from Lancet study) likely occur in U.S. as well

EPIDEMIOLOGY: HIGHWAY EMISSIONS CAUSE HIGH MORTALITY?

New Mann, et al study of IHD (ischemic heart disease) admissions, using 8 hour maximum average CO and O₃ data, 24 hour average NO₂ and PM₁₀ data, from 25-35 monitors in Los Angeles (“Air Pollution and Hospital Admissions for Ischemic Heart Disease...,” Env. Health Perspectives, 12/02):

* 1 ppm increase in 8 hr. ave. CO associated with:

- 3.60% increase in same-day IHD admission (w/secondary diagnosis of CHF)
- 2.99% increase in same-day IHD admission (w/secondary diagnosis of ARR)
- 1.62% increase in same-day IHD admission (w/no secondary diagnosis)

* NO₂ also significantly associated: NO₂ and/or CO effects, or are they surrogates for traffic pollutants?

* PM₁₀ never significantly associated

* Study somewhat similar to that of *Hoek, et al*, in that attempt is made to interpolate data from monitors to represent levels at people’s place of residence

EPIDEMIOLOGY: HIGHWAY PM, OR CO, CAUSES PREMATURE MORTALITY?

Carbon monoxide toxicology may suggest that some fraction of premature mortality association attributed to PM_{2.5} may be due to CO.

Rats exposed to 50 ppm CO for 1 hour (no lower level used) in Thom, et al, “Role of nitric oxide-derived oxidants in vascular injury from carbon monoxide in the rat,” Am. J. Physiol., 1999.

CO exposure effects:

- Increased capillary permeability
- Enhanced LDL oxidation
- Due to oxidative stress, “...results offer the first biochemical mechanism that may explain an association between atherosclerosis and chronic CO exposure...”

* Annual mean levels on major urban roads are ~ 10 ppm for 30 to 60 min. trip, winter levels double

POSSIBLE ACUTE CO LINK TO ACUTE CHD MORTALITY?

“Effect of Low-Level CO Exposure on Onset and Duration of Angina Pectoris” (Anderson, E.W., et al, Annals of Internal Medicine **79**, 1973:

50 ppm, 100 ppm CO tested on 10 adult men with stable angina pectoris. Results:

* “Mean duration of exercise before onset of pain was significantly shortened after both 50 and 100 ppm CO in comparison with air ($P < 0.005$).... EKGs recorded during and after exercise generally showed worsening of ST-segment changes, with earlier onset and longer duration of ST-segment depression. Low levels of CO can cause decreased exercise tolerance and worsening of myocardial ischemia in patients with angina pectoris.”

POSSIBLE ACUTE CO LINK TO ACUTE CHD MORTALITY?

- * Issue needs research – can't now conclude that CO at 10 to 20 ppm could cause CHD mortality
- * But possible toxicology link:

"...people with CHF would be more vulnerable to CO. CHF is of course the result of damage to the heart (usually by infarction - which usually is accompanied by narrowing of the vessels throughout the coronary circulation). The heart is very dependent on O₂ supply -- it has a high metabolic rate, can't stop to rest, and uses almost entirely aerobic metabolism. CO toxicity will tend to compromise O₂ delivery to heart muscle. It will also cause a need for greater cardiac output to supply O₂ to other tissues. Thus the heart is working harder at the same time as its O₂ supply is compromised. Results may be increased venous pressure, greater edema (esp. in lungs), and also arrhythmias because the electrolyte balance is disturbed in ischemic heart muscle leading to electrical problems."

EPIDEMIOLOGY: HIGHWAY PM CAUSES PREMATURE MORTALITY?

Janssen, et al, study (“Air conditioning and Source-Specific Particles as Modifiers of the Effect of PM10 on Hospital Admissions for Heart and Lung Disease,” EHP, Jan. 2002) – Results:

Multivariate analysis:

- For CVD: % PM10 from highway vehicles & diesels, oil combustion significant
- For COPD, pneumonia: similar pattern, associations less significant
- PM from coal combustion: small coefficients, far from significance
- AC has explanatory value: PM10 coefficients decreased significantly w/ increasing % of homes w/AC, when cities stratified by whether PM10 peaked in summer or winter

AMBIENT SULFATES: WHY DOES DOE SUGGEST NEGLIGIBLE PREMATURE MORTALITY EFFECTS?

Reasons of Epidemiology and of Toxicology

(1) Does epidemiology suggest sulfates more than, or less than PM_{2.5}?

- * PM and sulfate measures are virtually always highly correlated, statistics cannot attribute causation to either

- * 3 studies designed from start to see if sulfates, acidity were more highly associated with mortality than PM₁₀, PM_{2.5}: all 3 found the PM measures were more tightly linked (authors expressed surprise in 2 cases)

- * Newer epidemiological studies, with more sophisticated techniques, much more data, now tend to suggest highway emissions, not sulfate

- Anomalous results in major chronic studies (study finds that PM causes lung cancer only to poorly educated, or that CO is negatively and significantly correlated with premature mortality, for example)

Association Between Air Pollution and Mortality
- Dockery ET AL. - (Six Cities Study)

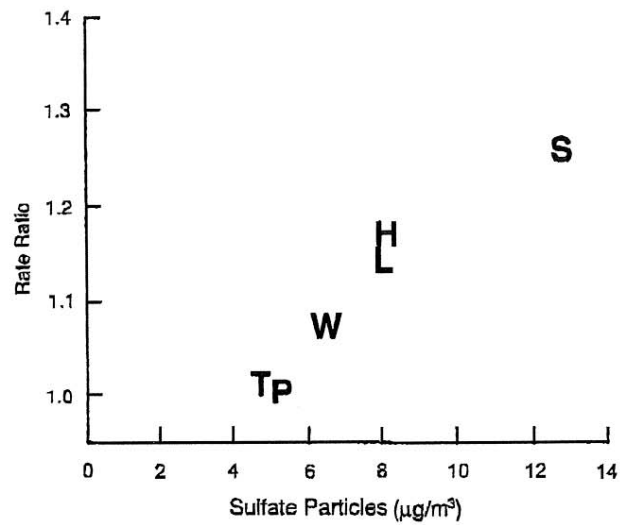
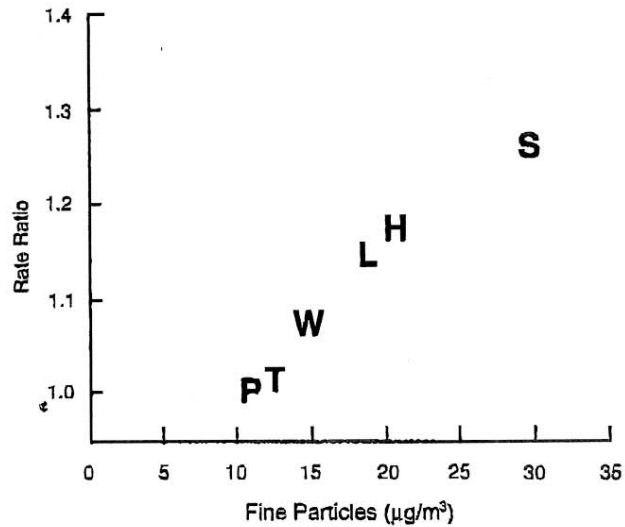


Figure 3. Estimated Adjusted Mortality-Rate Ratios and Pollution Levels in the Six Cities. Mean values are shown for the measures of air pollution. P denotes Portage, Wisconsin; T Topeka, Kansas; W Watertown, Massachusetts; L St. Louis; H Harriman, Tennessee; and S Steubenville, Ohio.

DOES EPIDEMIOLOGY SHOW THAT AMBIENT SULFATES CAUSE PREMATURE MORTALITY?

Examples from 2 of 3 studies designed from start to see if sulfates, acidity were more highly associated with mortality than PM₁₀, PM_{2.5} measures (1992 study design, findings ~ same as 2000 study below):

* “This epidemiological analysis suggest that fine particle mass is specifically associated with increased daily mortality. It suggests that these associations are not attributable to the sulfate or acidic composition of these particles.” (Schwartz, J. et al, J. Air & Waste Manage. Assn., 1996)

* “...the PM mass indices were more significantly associated with health outcomes than H⁺ or SO₄. As the investigators pointed out, this result is inconsistent with their original hypothesis regarding the role of acidity in the air pollution-mortality relationship.” (Lippmann, M, et al, HEI, 2000)

DOES EPIDEMIOLOGY SHOW THAT AMBIENT SULFATE (OR HIGHWAY PM) CAUSE PREMATURE MORTALITY?

ACS study: SO₄, PM correlation; also, PM, sulfate assn. with cardiovascular, lung cancer mortality. But...

- * Only those with less education so affected – is this likely, especially for lung cancer?
- * Could sulfate cause lung cancer? Dr. Bruce Ames, inventor of test for potential carcinogenicity, states “neither ammonium or sulfate is likely to be a mutagen or carcinogen. They are in the medium for the bacteria normally and are used in metabolism.”
- * Cambridge Environmental, Inc. (Feb. 2002):
 - Using data from Krewski, et al (HEI) reanalysis of ACS, Six Cities studies, CEI finds that sulfate would be 1.7 times more potent a lung carcinogen than coke oven emissions – is this feasible, given sulfate’s presence in several asthma and COPD inhalers?
 - Bayer’s statin drug, Baycol, was found to have caused death of 100 people in 5 years, out of 750,000 peak users – if sulfate caused cancer, wouldn’t we know from millions of inhaler users?

DOES EPIDEMIOLOGY SHOW THAT AMBIENT SULFATE (OR HIGHWAY PM) CAUSE PREMATURE MORTALITY?

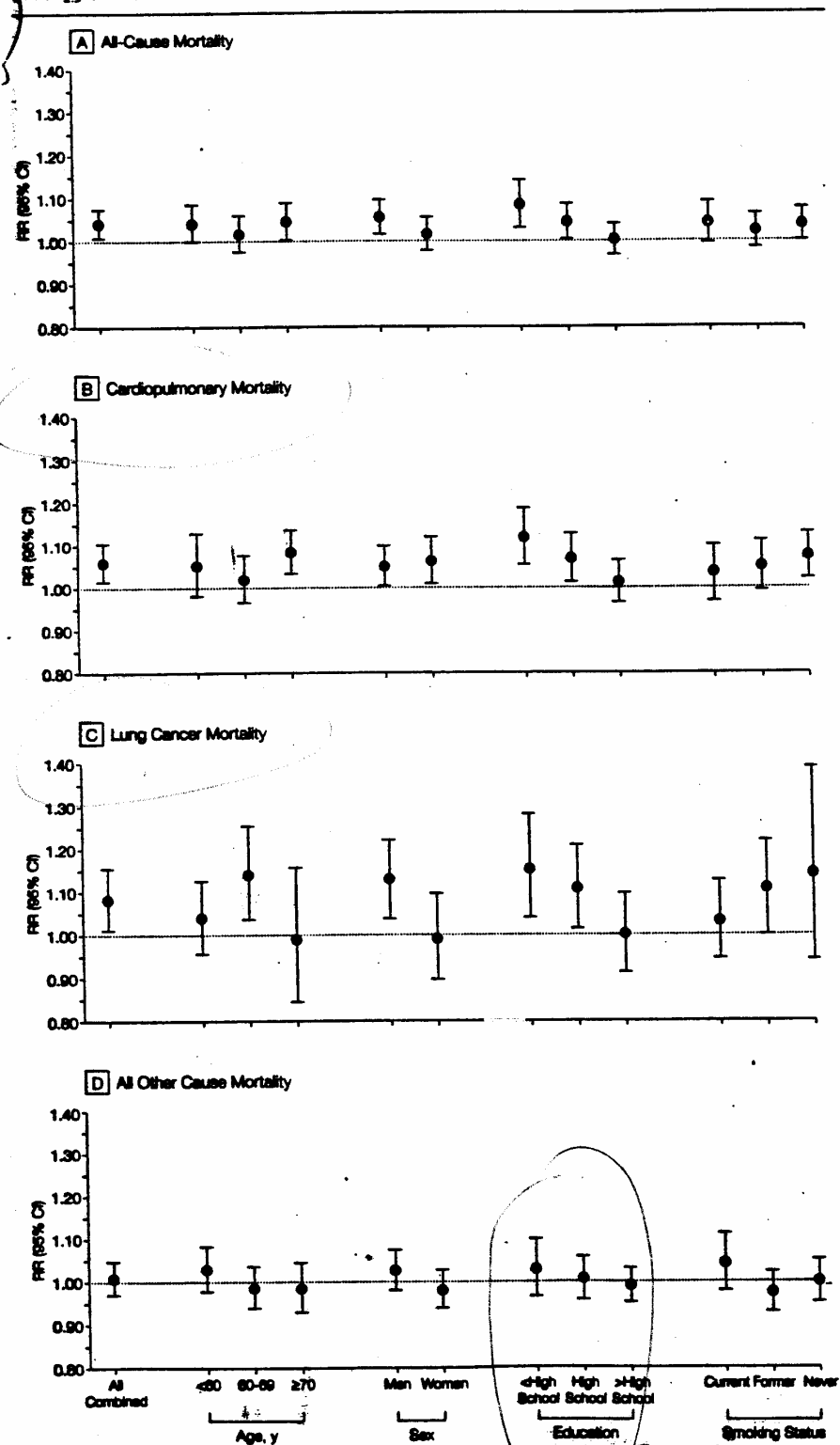
* ACS finds CO negatively and significantly associated with premature mortality – with new, post-Oct. 2002 evidence, such a finding appears to be *a priori* evidence that study's self described limitations (single monitor) is preventing study from finding correct associations

* Alternative explanations for lung cancer, CVD results (not mutually exclusive):

- 0 Since enrollment in 1982, more of better educated people ceased smoking
- 0 Diesel/highway emissions?

Explanation: larger SMSAs with more traffic, more PM_{2.5}, more diesel, and more poor and uneducated, all toward city centers (on average), may have more cardiopulmonary mortality and lung cancer than smaller SMSAs. Single monitor studies, unable to examine highway proximity, instead find association with higher PM_{2.5}, SO₄ levels in larger SMSAs.

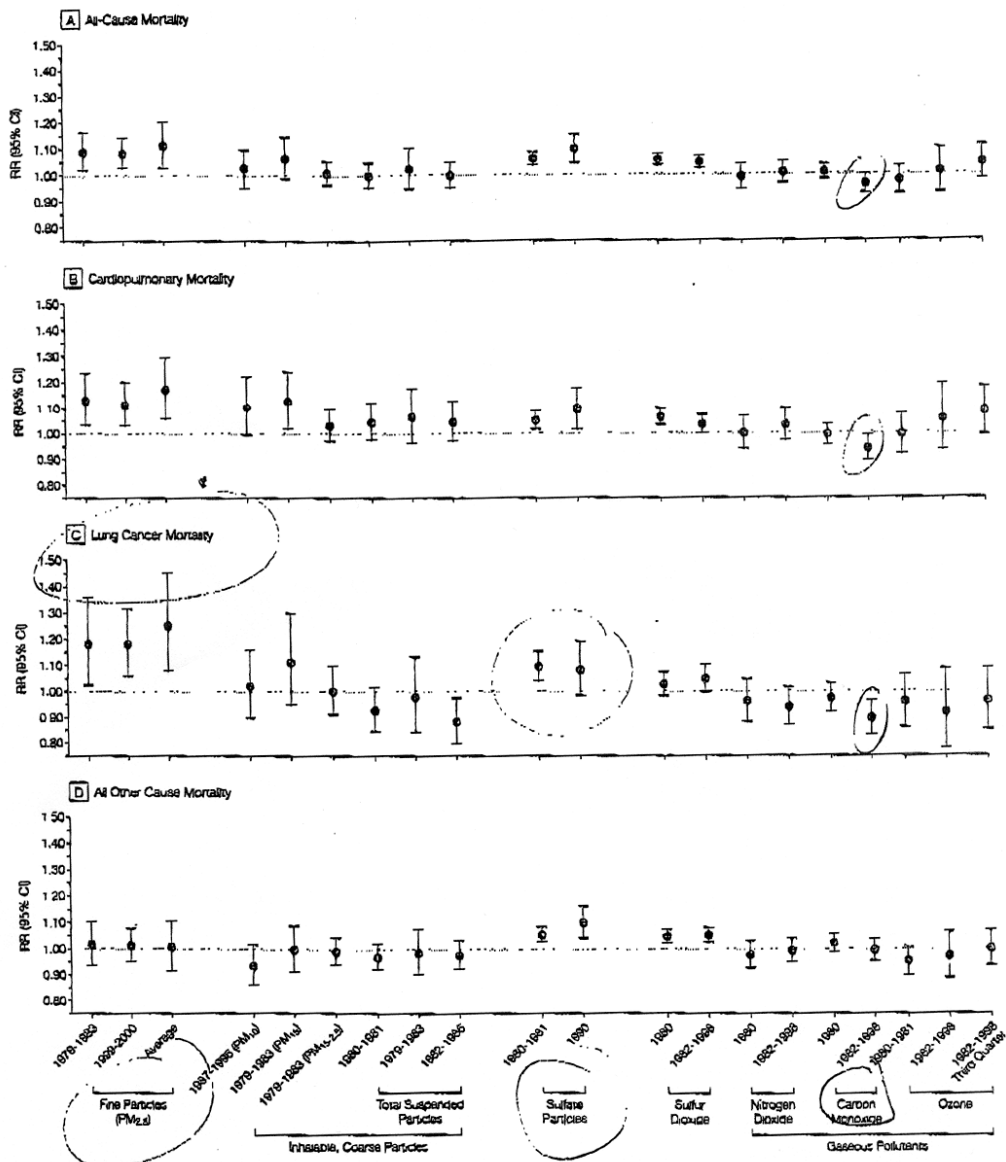
Figure 4. Adjusted Mortality Relative Risk (RR) Ratio Associated With 10- $\mu\text{g}/\text{m}^3$ Differences of $\text{PM}_{2.5}$ Concentrations



Data presented are for 1979-1983 for the different causes of death stratified by age, sex, education, and smoking status. $\text{PM}_{2.5}$ indicates mean fine particles measuring less than $2.5\text{ }\mu\text{m}$ in diameter; CI, confidence interval.

MORTALITY AND LONG-TERM EXPOSURE TO AIR POLLUTION

Figure 5. Adjusted Mortality Relative Risk (RR) Ratio Evaluated at Subject-Weighted Mean Concentrations



PM_{2.5} indicates particles measuring less than 2.5 μ m in diameter; PM₁₀, particles measuring less than 10 μ m in diameter; PM₁₅, particles measuring less than 15 μ m in diameter; PM_{2.5-10}, particles measuring between 2.5 and 15 μ m in diameter; and CI, confidence interval.

TOXICOLOGY OF SULFATES

EPA: April, 2002 CD, pg. 9-70: “The epidemiological results suggest the need for toxicological studies of the sulfate, nitrate, and organic components of PM, including studies with compromised or susceptible individuals.”

EPA: April, 2002 CD, Toxicology Chapter: subsections on 7 types of PM_{2.5}, sulfates not among them

But while there aren't many, there are a few studies of sulfates and premature mortality...

TOXICOLOGY OF SULFATES (Cont.)

(1) Ehrlich, R, et al, “Susceptibility to Bacterial Pneumonia of Animals Exposed to Sulfates,” Toxicology Letters, 1978:

- No increase in rodent mortality from respiratory pathogen after 3 hour exposure to up to 5.3 milligrams/m³ (NH₄)₂SO₄ (highest level tested)
- No increase in rodent mortality after exposure to 1.1 milligrams/m³ or less of ZnSO₄; increase did occur at 1.3 milligrams and above (ave. annual PM_{2.5} Zn levels in major US cities, 2000-2002, from ~10 to ~40 nanograms/m³)

TOXICOLOGY OF SULFATES (Cont.)

(2) Sackner, M et al, “Effects of Brief and Intermediate Exposures to Sulfate Submicron Aerosols...”, J. Toxicol. and Env. Health, 1981:

* After 4 hour inhalation (in dogs) of between 4.1 and 8.8 milligrams/m³ of 12 sulfates (mostly sulfates of Fe, Cu, Ni, Zn, Mn, Al, NH₄), “...no significant alterations in total respiratory resistance, functional residual capacity, static lung compliance, and specific total respiratory conductance...Further, there were no significant alterations in mean pulmonary arterial and carotid arterial pressures, cardiac output, heart rate, stroke volume, arterial pH and arterial O₂ and CO₂ tensions.”

* Compare with CAPs studies – far lower amounts of Boston PM caused changes in HRV, heart rate (on ~ 75% of days – on 25% of days, no effects at all, as PM appeared to be missing toxic constituent[s])

TOXICOLOGY OF SULFATES (Cont.)

(3) Several asthma inhalers use sulfate (albuterol, terbutaline, metaproterenol sulfates): asthmatic will commonly inhale 10,000 micrograms/m³ sulfate 6 to 8 times daily.

Suggests that ambient sulfates aren't inherently toxic (but can't prove that sulfates can't be harmful in combinations, even at far lower ambient levels – that's why we need uniform tests)

Sulfate also used in an inhaler for COPD (chronic bronchitis and emphysema)

Sulfates also part of medicines:

- to stabilize heart after ischemic events, and for migraines (magnesium sulfate)
- part of some antibiotics
- used to treat malaria (Plaquenil sulfate)
- for eclampsia and toxemia of pregnancy (magnesium sulfate)
- to prevent deep vein thrombosis after surgery (dermatan sulfate)

WOOD SMOKE

* Little research has been done, but tests show 4 X respiratory mortality in rodents exposed to levels of smoke not much different than from indoor (wood stove or fireplace), vs. 2 controls

* Compare with *Ehrlich, et al* results (also respiratory mortality): wood smoke can kill at near ambient indoor levels and at ~ 400 times wintertime outdoor ambient in the Southeastern U.S., vs. zinc sulfate at ~10,000 times outdoor ambient

Only beginning to understand levels of wood smoke in ambient air:

- ~ 10% of total space heating input in US from firewood
- High percentage (~ 70%) of outdoor wood smoke from chimneys reenters house and permeates neighboring dwellings
- Wood smoke 40% of wintertime PM in Santa Clara country (San Jose area), 50% to 85% of wintertime PM in Pacific NW, 20% of wintertime PM in Southeast U.S.

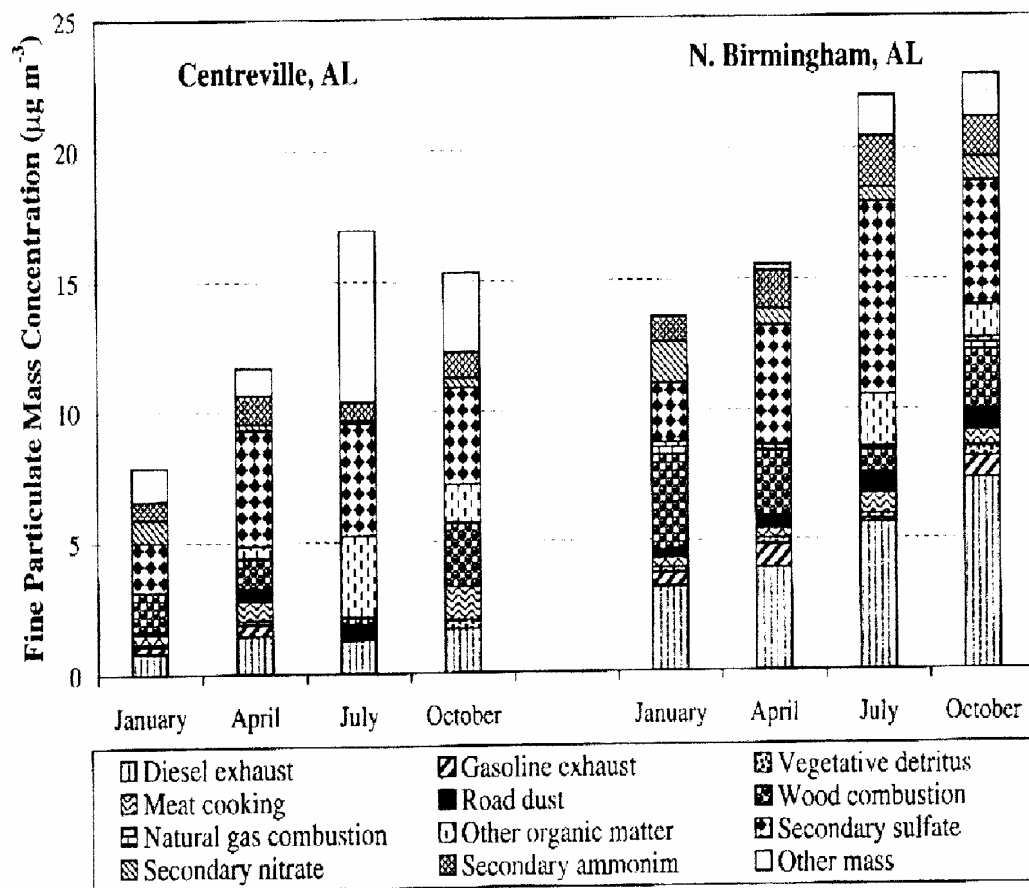
WOOD SMOKE (Cont.)

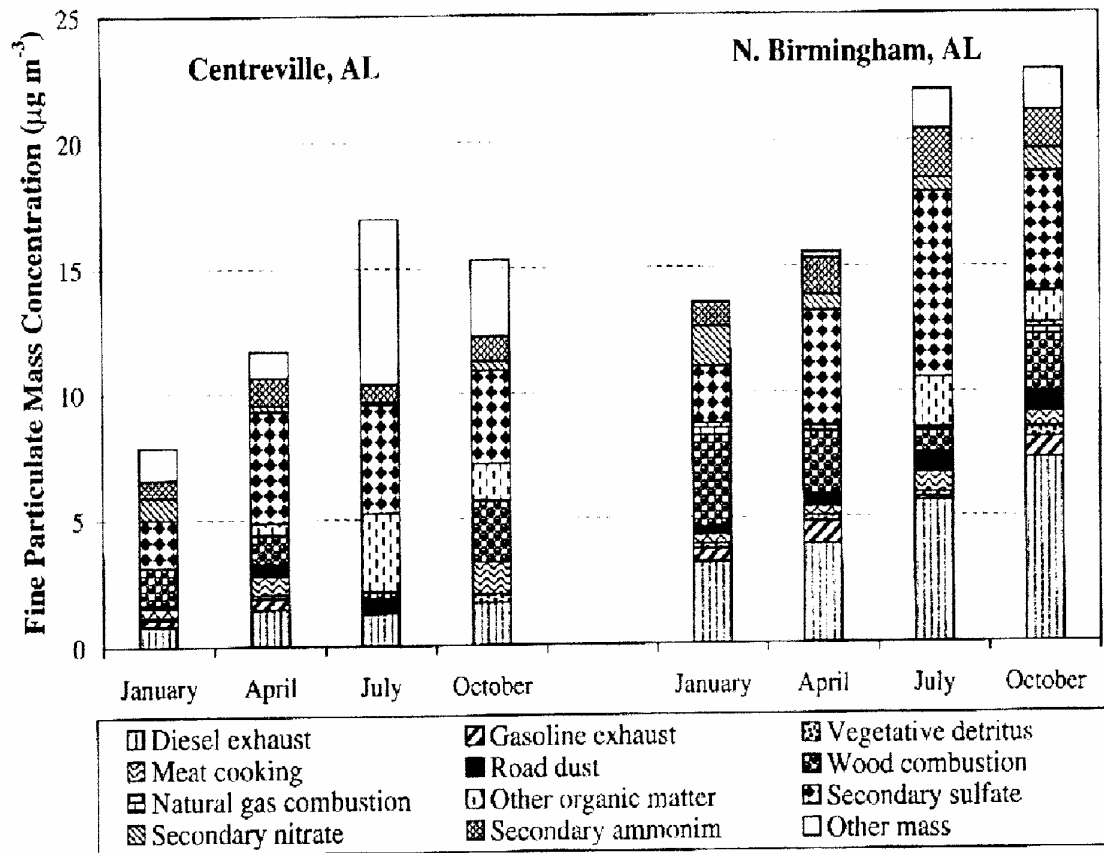
Wood smoke toxicology just beginning (caveat: research results at several thousand times typical exposures must always be viewed with caution, for wood smoke, sulfates, diesel, anything else):

Zelikoff, et al, 2002 review article -- “The Toxicology of Inhaled Woodsmoke, J. Toxicol. & Env. Health”:

- Effects include increased microvascular permeability, pulmonary edema
- Nectrotizing tracheobronchial epithelial cell injury
- Possible increase in lung cancer incidence in mice
- Compromised pulmonary macrophage-mediated immune mechanisms

Source Contributions to Organic Carbon in Fine Particles





METALS

Metal (from AIRS data, 2001 nanograms/m³)

Location	V	Zn	Ni	Fe	Cu
NYC (Bronx)	7	30	31	112	4
NYC (Queens)	6	25	11	107	3
Elizabeth, NJ (at tnpk. xchng.)	6	17	4	121	6
Baltimore	3	21	2	113	4
St. Louis	2	30	2	235	14
Bakersfield, CA	1	9	2	164	11
San Jose, CA	2	10	15	146	4
Riverside, CA	6	24	3	171	5
Boston	5	12	5	85	2
Chicago	1	42	1	142	7
Westport, Conn. (near tnpk.)	1	4	1	42	10

Note: In Six Cities study, Boston V level, 1979-1986, was 23.2 nanograms/m³, and Ni level was 8.8 nanograms/m³ -- use of residual fuel oil clearly down. St. Louis Six Cities study V and Ni levels unchanged.

METALS

* *In vivo* installation tests have shown significant cardiopulmonary (inflammatory) injury from high levels of ROFA (residual oil fly ash), high levels of urban PM in some locations: effects due to bioavailable transition metals

* *In vivo* installation tests of aqueous extracts of PM from filters in Utah valley (near poorly controlled steel mill in 1980s) showed inflammatory lung injury

* Fernandez, et al inhalation study (“Resuspension of coal...generated fine particles....,” Science of the Total Environment, 2002) finds that zinc in particles in municipal sewage, burned in conjunction with coal, causes increased lung permeability and decreased cells counts (1,000 ug/m³ and higher), but coal ash not associated (3,000 ug/m³) with these health end points, despite higher iron levels than sewage/coal combination (and despite *in vitro* findings that suggested coal ash would cause these adverse effects)

METALS (Cont.)

* Under what circumstances are metals bioavailable?

- Solubility (many ways to make soluble, incl. sulfates; for ROFA, metals appear to be made soluble by sulfates produced in combustion process itself)
- Insoluble metals bioavailable as well: study in Utah (“Metals Associated with Both the Water-Soluble and Insoluble Fractions...,” Ghio, et al, Inhalation Toxicol., 11, 1999) states that:
 - * “...larger total quantities of catalytically and biologically active metals are likely to be associated with the insoluble fraction as a result of the abundance of the latter...”
 - “Water-soluble metals are likely to be removed from the lower respiratory tract at a faster rate than metals included in the insoluble components of the particle...those metals included in the water-insoluble fraction may assume a greater importance in the persistence of radical generation and tissue damage.”

METALS (Cont.)

Pritchard, R.J., et al (“Oxidant generation and lung injury after particulate air pollutant exposure increase with the concentrations of associated metals,” Inhalation Toxicology, 1996) installation study of several urban dusts, fly ashes:

“The majority of iron associated with the dusts was not easily solubilized by aqueous solutions (i.e., the metal was not present as a soluble salt). It is therefore likely that atmospheric particulates other than sulfates also have a capacity to coordinate metals. Functional groups on the particulates that can serve as ligands in the coordination of metals include the hydroxyl groups of mineral oxides in aqueous media and the carboxylate and phenol groups of incompletely oxidized carbon fragments.”

METALS (Cont.)

Bottom line:

- * Are PM2.5 metals likely to cause minimal mortality? Localized mortality (near ROFA, steel mills)? More widespread? Should there be a PM2.5 metals standard?
- * Which metals may be problematic? Sources?
- * To what extent do these metals cause effects without being solubilized? To what extent are they solubilized *in vivo* by regional sulfates? Solubilized by other chemistry? (ROFA = special case, V and Ni already solubilized as they exit stack, can't be solubilized a second time outside stack)

To the extent that various metals may be a problem, what should be reduced to reduce possible mortality impacts, if any, from metals?

COAL FLY ASH A PROBLEM?

New HEI study (12/02) suggests iron from CFA can cause inflammatory response (IL-8) in cultured (*in vitro*) human lung epithelial cells, that iron on CFA surface may be responsible, and that sulfates make iron more bioavailable – to what extent does this mean that CFA might cause premature mortality in ambient concentrations?

- *In vitro* findings may not occur *in vivo* – e.g., Fernandez, et al results previously reviewed (lung injury with *in vitro* tests of CFA, but not *in vivo* at 3,000 ug/m³)
- Example: Humans exposed to CAPs in Chapel Hill, up to 311 ug/m³, showed no increase in IL-8, major CFA inflammatory response at high levels in HEI study – suggests little effect from ambient CFA (Ghio, et al, Am J Respir Crit Care Med, V 162, 2000)
- Iron levels very different: HEI study (depending on assumptions) appear to be equivalent of over 1,000 ug/m³ CFA inhaled, but ambient CFA levels are usually < 100 nanograms/m³
- Ambient iron levels in large cities usually between 100 and 200 ng/m³ today; iron levels from CFA < 8 ng/m³
- Also recall Pritchard, et al: ambient iron not easily solubilized by aqueous solutions such as sulfates

PROF. R. SCHLESINGER REVIEW OF TOXICOLOGY OF ATMOSPHERIC SECONDARY INORGANIC PM

* Annex B of Netherlands report on health risks of PM_{2.5} (42 pgs., prepared Feb. 2002)

- Toxicological effects, where they exist, are for very high acidity levels, not for nitrate or sulfate anion
- No effects from ambient acidity levels, however: likely a threshold for acidity effects due to ammonia neutralization in respiratory tract
- “There are likely no adverse or irreversible effects, as far as cardiopulmonary function is concerned, from ambient levels of sulfate or nitrate aerosols, even in presumably more sensitive asthmatics.” (pg. B-28)
- “To the extent that they have been evaluated, toxicological studies of these constituents..., as well as metal sulfates and nitrates and ammonium bisulfate, suggest there to be little toxic potency at [environmentally relevant concentrations]...”

“ON HEALTH RISKS OF AMBIENT PM IN THE NETHERLANDS”

- * General conclusion: to control PM types which may cause premature mortality, control of vehicular emissions is more likely to bring benefit than control of secondary sulfates, nitrates
- * Quote: “Further source-oriented actions could focus on reduction of the total PM₁₀ aerosol mass or, first of all, on those PM fractions that are expected to be more health-relevant. This last option is preferred. These fractions are probably transport-related (diesel soot) and, more generally, combustion related primary PM emissions.”
 - Health risks (relative risk of mortality) have not come down (higher but insignificantly so), while sulfate levels have decreased by a factor of 5 from the mid-1980s (personal communication with one of the study’s authors)

SUMMARY

- * In late 1980s, early 1990s, we measured PM mass, sulfates, and various gases (for most part)
- * Given high correlation between PM mass and sulfate, both were associated with premature mortality at the time – some researchers also advanced thesis that acidity was at fault
- * Now, we measure more PM types (ARIES), have more sophisticated studies (Hoek, et al; Janssen, et al; Mann, et al;), see huge local PM variation that is co-located with huge relative risk of cardiopulmonary mortality, and understand that current acidity levels unlikely to cause harm
- * To reduce premature mortality from PM (and associated gases?), tremendous research need for “Structured Regulatory Toxicology Program”
 - In absence of such a program, evidence appears to point strongly toward control of diesel, vehicular emissions, but still need to know *which* emissions